Alpha 1 Antitrypsin MZ Information & Research

News & Research Update

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Website status and research update

Dear subscribers,

This week we got a question about Fatty Liver in relation to Alpha1 MZ.

As many of us know, most of the Alpha1 MZ patients have a fatty liver, and you (and your MD) may not be aware of the root cause, and the relationship with Alpha1 MZ.

As explained in previous News & Research updates, the PiMZ liver is affected by the AAT “Z” protein accumulation in the ER of the Hepatocyte, forming polymers and causing Hepatocyte ER stress. Being an Alpha1 MZ, the Recruitment Secretory Block plays a role as well, meaning that all three zones of the liver lobules may be affected. (Periportal, Midlobular and Pericentral)

Because the Hepatocyte ER plays a crucial role in fatty acid synthesis and cholesterol metabolism, and the fact that the Hepatocyte ER is under continuous stress in a PiMZ liver, there is a very high prevalence of Alpha1 MZ’s with a fatty liver. I don’t have Biobank data (yet), but my personal observation is that all Alpha1 MZs over 40 years of age experience a fatty liver, and recently a 10 year old MZ child was diagnosed with a fatty liver.

Please also note that a fatty liver causes more degradation of the already reduced functional capacity of the PiMZ liver.

The paper below explains the relationship between ER stress and Fatty Liver. Below is a small but important part of this paper from 2023.

Unfolded Protein Response Signaling in Liver Disorders: A 2023 Updated Review

“The endoplasmic reticulum (ER) is the site for synthesis and folding of secreted and transmembrane proteins. Disturbance in the functioning of ER leads to the accumulation of unfolded and misfolded proteins, which finally activate the unfolded protein response (UPR) signaling. The three branches of UPR—IRE1 (Inositol requiring enzyme 1), PERK (Protein kinase RNA-activated (PKR)-like ER kinase), and ATF6 (Activating transcription factor 6) modulate the gene expression pattern through increased expression of chaperones and restore ER homeostasis by enhancing ER protein folding capacity."

“There is a direct relationship between ER stress and fatty liver, as ER plays a crucial role in fatty acid synthesis and in cholesterol metabolism. Hence, chronic ER stress may promote fatty liver disease.ER stress also causes steatosis (fat accumulates in the liver cells) by disrupting lipid secretion.”